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10/576,631	04/16/2007	Stephen O'Hara	63162US005	5768

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/576,631	O'HARA, STEPHEN	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/8/09 has been entered. The instant claim amendments are acknowledged.

Claims 1-19 are pending and under examination.

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. The rejection of claims 1-10 and 13-15 under 35 U.S.C. 102(b) as being anticipated by Peck et al. US 5,789,173 Aug. 4 1998 is maintained.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-

organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species
wherein steps (a) and (b) are performed by analyzing the micro-organism's
nucleic acid.

As to claim 1, Peck et al teaches a process for analyzing a biological sample (human body fluids, blood), comprising:

Incubating specimens of said samples in media embedded with antimicrobial agents of serial dilution concentration (pre-determined concentration) for a short time (pre-determined time period) to create differential microbial counts and amplifying the differential microbial counts by in vitro microbial DNA replication (assessing the number of microorganisms in the sample at the end of the pre-determined time period and analyzing the micro-organism's nucleic acid). See column 3 lines 18-34 and lines 56-61. Peck teaches step instant step (a) involving identifying a microorganism present within said sample by analyzing the microorganism's nucleic acid in column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no

antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed".

As to the instant claim limitation "wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species", identification of a microorganism in the sample as taught by Peck et al *is* an identification of the species of the microorganism identified. The is because a microorganism identified is will necessarily be a micro-organism species.

As to claim 2-5, Peck et al teaches step a and step involving nucleic acid hybridization assay involving DNA amplification from the microorganism using polymerase chain reaction PCR. See DNA amplification primers in column 4 lines 38-45, column 5 lines 56-67 to column 6 lines 1-4, column 10 claims 1 and 11-13).

As to claim 6, Peck et al teaches primers specific to microorganism of interest column 4 lines 38-45 and column 10 claims 17-18.

As to claim 7-9, Peck et al teaches analyzing of the microorganism's DNA and teaches analysis of the 16S rRNA by analysis of the 16s rRNA gene. See column 10 claim 17...wherein in vitro DNA replication amplifies a target DNA nucleotide sequence which encodes for the 16S rRNA gene.

As to claim 10, Peck et al teaches step A as set forth above and teaches that specimens from different human systems require different treatments and teaches the removal of pathogens from blood and precipitation of pathogens from blood (column 4 lines 46-47 and lines 52-58).

As to claim 13, Peck et al teaches instant step a and instant step as set forth above and teaches comparison step a and step b : column 2 lines 17-21… "identification of the pathogen,

however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed" (i.e. a control well without antibiotics but with DNA amplification primers specific for fungi and mycobacteria).

As to claim 14, Peck et al teaches that the microorganism is a fungi or a bacterium: column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed"

As to claim 15, Peck et al teaches that the antimicrobial is an antibiotic or an antimycotic (antifungal such as fluconazole, nystatin or amphotericin b). See column 4 lines 24-33).

Applicants' arguments:

Claim 1 is currently amended to include the feature "wherein identifying a micro-organism present in the sample comprises identifying a micro-organism species". Support for the amendment can be found in the application on page 9, line 27, to page 10, line 15. Peck et al. does not teach or suggest identifying a microorganism species. Therefore, claim 1, as amended, is novel over Peck et al. Claims 2-15 each add additional features to claim 1 and are likewise novel over Peck et al.

In amending claim 1, Applicant does not acquiesce to the Examiner's rejection of all original dependent claims. For example, the Examiner alleges that claim 8 is anticipated by Peck et al. Applicant disagrees. Peck discloses the detection of DNA such as the 16S rRNA gene (see, for example, column 5, lines 15-16).

The response:

Applicants' arguments are carefully considered but are not persuasive.

As to the instant claim limitation "wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species", identification of a microorganism in the sample as taught by Peck et al *is* an identification of the species of the microorganism identified. This is because a microorganism identified is necessarily a micro-organism species.

As to analysis of the micro-organisms RNA or rRNA, Peck et al teaches analysis of the 16S rRNA via analysis of the 16S rRNA gene. See column 10 claim 17...wherein in vitro DNA replication amplifies a target DNA nucleotide sequence which encodes for the 16S rRNA gene. Instant claims 8 and 9 do not specify exactly how the RNA or rRNA is analyzed and thus analysis of the 16S RNA gene as taught by Peck et al is an indirect analysis of the 16S rRNA.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. The rejection of claims 1-10, 12 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Peck et al. US 5,789,173 Aug. 4 1998 is maintained.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's nucleic acid.

As to claim 1, Peck et al teaches a process for analyzing a biological sample (human body fluids, blood), comprising:

Incubating specimens of said samples in media embedded with antimicrobial agents of serial dilution concentration (pre-determined concentration) for a short time (pre-determined time period) to create differential microbial counts and amplifying the differential microbial

counts by in vitro microbial DNA replication (assessing the number of microorganisms in the sample at the end of the pre-determined time period and analyzing the micro-organism's nucleic acid). See column 3 lines 18-34 and lines 56-61. Peck teaches step instant step (a) involving identifying a microorganism present within said sample by analyzing the microorganism's nucleic acid in column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed".

As to the instant claim limitation "wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species", identification of a microorganism in the sample as taught by Peck et al *is* an identification of the species of the microorganism identified. The is because a microorganism identified is will necessarily be a micro-organism species.

As to claim 2-5, Peck et al teaches step a and step involving nucleic acid hybridization assay involving DNA amplification from the microorganism using polymerase chain reaction PCR. See DNA amplification primers in column 4 lines 38-45, column 5 lines 56-67 to column 6 lines 1-4, column 10 claims 1 and 11-13).

As to claim 6, Peck et al teaches primers specific to microorganism of interest column 4 lines 38-45 and column 10 claims 17-18.

As to claim 7-9, Peck et al teaches analyzing of the microorganism's DNA and teaches analysis of the 16S rRNA by analysis of the 16s rRNA gene. See column 10 claim 17...wherein in vitro DNA replication amplifies a target DNA nucleotide sequence which encodes for the 16S rRNA gene.

As to claim 10, Peck et al teaches step A as set forth above and teaches that specimens from different human systems require different treatments and teaches the removal of pathogens from blood and precipitation of pathogens from blood (column 4 lines 46-47 and lines 52-58).

As to claim 13, Peck et al teaches instant step a and instant step as set forth above and teaches comparison step a and step b : column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed" (i.e. a control well without antibiotics but with DNA amplification primers specific for fungi and mycobacteria).

As to claim 14, Peck et al teaches that the microorganism is a fungi or a bacterium: column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed"

As to claim 15, Peck et al teaches that the antimicrobial is an antibiotic or an antimycotic (antifungal such as fluconazole, nystatin or amphotericin b). See column 4 lines 24-33).

As to claim 12, Peck et al differs in that the reference does not teach that antimicrobials used in step (b) are selected based on the results of step a.

However, the invention of claim 12 would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made based on the teachings of Peck et al. Since Peck et al teaches antimicrobial susceptibility testing and teaches that in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested, two micro-wells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed, it would have been prima facie obvious to first distinguish whether the samples contain fungi or mycobacteria using the microorganism specific DNA amplification primers and then perform the antimicrobial susceptibility testing using antifungal or antibiotic depending on the results of the DNA amplification. The method of Peck et al is modified in this manner to save time and resources (antimicrobials) in that the right type of antimicrobial (antifungal vs. antibiotic) is used for the antimicrobial susceptibility testing.

Applicants' arguments:

Claim 1 is currently amended to include the feature "wherein identifying a micro-organism present in the sample comprises identifying a micro-organism species". Support for the amendment can be found in the application on page 9, line 27, to page 10, line 15. Peck et al. does not teach or suggest identifying a microorganism species. Therefore, claim 1, as amended, is novel over Peck et al. Claims 2-15 each add additional features to claim 1 and are likewise novel over Peck et al.

The response:

Applicants' arguments are carefully considered and are for essentially the same reasons set forth above. The arguments are not persuasive and have been addressed as set forth above.

3. The rejection of claims 1-11 and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Peck et al. US 5,789,173 Aug. 4 1998 in view of Bruno et al. Journal of Molecular Recognition, Vol. 9, 474-479 (1996) cited in IDS is maintained.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's nucleic acid.

As to claim 1, Peck et al teaches a process for analyzing a biological sample (human body fluids, blood), comprising:

Incubating specimens of said samples in media embedded with antimicrobial agents of serial dilution concentration (pre-determined concentration) for a short time (pre-determined time period) to create differential microbial counts and amplifying the differential microbial counts by in vitro microbial DNA replication (assessing the number of microorganisms in the sample at the end of the pre-determined time period and analyzing the micro-organism's nucleic acid). See column 3 lines 18-34 and lines 56-61. Peck teaches step instant step (a) involving identifying a microorganism present within said sample by analyzing the microorganism's nucleic acid in column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed".

As to the instant claim limitation "wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species", identification of a microorganism in the sample as taught by Peck et al *is* an identification of the species of the microorganism identified. The is because a microorganism identified is will necessarily be a micro-organism species.

As to claim 2-5, Peck et al teaches step a and step involving nucleic acid hybridization assay involving DNA amplification from the microorganism using polymerase chain reaction PCR. See DNA amplification primers in column 4 lines 38-45, column 5 lines 56-67 to column 6 lines 1-4, column 10 claims 1 and 11-13).

As to claim 6, Peck et al teaches primers specific to microorganism of interest column 4 lines 38-45 and column 10 claims 17-18.

As to claim 7-9, Peck et al teaches analyzing of the microorganism's DNA and teaches analysis of the 16S rRNA by analysis of the 16s rRNA gene. See column 10 claim 17...wherein in vitro DNA replication amplifies a target DNA nucleotide sequence which encodes for the 16S rRNA gene.

As to claim 10, Peck et al teaches step A as set forth above and teaches that specimens from different human systems require different treatments and teaches the removal of pathogens from blood and precipitation of pathogens from blood (column 4 lines 46-47 and lines 52-58).

As to claim 13, Peck et al teaches instant step a and instant step as set forth above and teaches comparison step a and step b : column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed" (i.e. a control well without antibiotics but with DNA amplification primers specific for fungi and mycobacteria).

As to claim 14, Peck et al teaches that the microorganism is a fungi or a bacterium: column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two microwells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed"

As to claim 15, Peck et al teaches that the antimicrobial is an antibiotic or an antimycotic (antifungal such as fluconazole, nystatin or amphotericin b). See column 4 lines 24-33).

Although Peck teaches the removal of pathogens from blood and precipitation of pathogens from blood (column 4 lines 46-47 and lines 52-58), Peck et al does not teach removal of pathogens/microorganisms from blood by immunomagnetic separation.

Bruno et al teaches that immunomagnetic separation and concentration of specific target ligands or particles, such as bacteria ... from complex mixtures such as ... blood… is a widely accepted technique. See first sentence of abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to separate pathogen/microorganisms from blood in the method of Peck et al using immunomagnetic separation because Bruno et al teaches that immunomagnetic separation and concentration of specific target ligands or particles, such as bacteria from complex mixtures such as blood is a known and widely accepted technique. Thus, resulting in the instant invention with a reasonable expectation of success.

Applicants' arguments:

Claim 1 is currently amended to include the feature "wherein identifying a micro-organism present in the sample comprises identifying a micro-organism species". Support for the amendment can be found in the application on page 9, line 27, to page 10, line 15. Peck et al. does not teach or suggest identifying a microorganism species. Therefore, claim 1, as amended, is novel over Peck et al. Claims 2-15 each add additional features to claim 1 and are likewise novel over Peck et al.

The response:

Applicants' arguments are carefully considered and are for essentially the same reasons set forth above. The arguments are not persuasive and have been addressed as set forth above.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, step b) clearly sets forth the process for determining the effect of one or more antimicrobial(s) on a microorganism from the sample by adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period.

However, the claims also recites that step b) is performed by analyzing the microorganisms nucleic acid. It is not clear how step b) is performed by two different processes in the claim, since earlier in the claim, the process of performing step b) i.e. determination of effect of one or more antimicrobial(s) on a microorganism from the sample is set forth. If

Applicants intend that analysis of the microorganisms nucleic acid is additional to the process set forth in step b), this is not clear in the claim.

Claim 18 recites "determination of at least a part of the microorganism's genome sequence". It is not clear how "at least a part of the microorganism's genome sequence is determined. Claim 19 recites "determination of restriction fragment length polymorphism or amplified rDNA restriction analysis" It is not clear how "restriction fragment length polymorphism or amplified rDNA restriction analysis" is determined. Does Applicant mean that analysis of the microorganism's nucleic acid is carried out by restriction fragment length polymorphism or amplified rDNA restriction analysis? "Determination" as used in claims 18 and 19 implies a mental step and the claims do not clearly set forth the process underlying the "determination".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 4, 5, 6, 7, 12-15, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Cooksey et al. Journal of Clinical Microbiology, May 2002, p. 1651-1655/

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's nucleic acid.

Cooksey et al teaches a process for analyzing a biological sample, comprising the steps of

-identifying a microorganism present in specimen samples from patients (see p. 1652 column 1 under "bacterial isolates" and "nucleic acid procedures")

-determining the effect of one or more antimicrobial e.g. antibiotics on a microorganisms from the sample by adding said antimicrobials at predetermined concentration to a sample, incubating the sample in the presence of said antimicrobials for a predetermined time period under conditions that allow some growth of the microorganism (i.e. plating on Middlebrook and Cohn 7H10 agar containing the antimicrobials), and assessing the number in the sample at the end of the pre-determined period (see p. 1652 column 1 under "antimicrobial susceptibility testing" and p. 1652 column 2 table 1);

-wherein identifying a microorganism present in the sample comprises identifying a microorganism species by PCR (polymerase chain reaction) or PCR-RFLP (PCR-restriction

fragment length polymorphism), in the instant case Cooksey et al identifies *Mycobacterium bovis* and *Mycobacterium tuberculosis* in samples collected from patients (see p. 1652 p. 1652 column 1 under "bacterial isolates" and "nucleic acid procedures" and first paragraph under "results" section)

-wherein steps (a) and (b) are performed by analyzing the microorganisms nucleic acid. See p. 1652 table 1 for analysis of the antimicrobial resistance of *Mycobacterium tuberculosis complex* (MTC) nucleic acid compared to the RFLP pattern.

As to claim 2, Cooksey et al teaches a nucleic acid hybridization assay (PCR or PCR-RFLP) for identifying the microorganism in the samples.

As to claim 4-6, Cooksey et al teaches instant step (a) as set forth above involving amplification of nucleic acid from the microorganism (PCR or PCR-RFLP) using primers specific to the Mycobacteria of interest. See p. 1652 column 1 under "nucleic acid procedures".

As to claim 7, the process of Cooksey et al as set forth above teaches analysis of the microorganisms DNA. See p. 1652 table 1 for RFLP.

As to claim 12, Cooksey et al teaches that the types of Mycobacteria species in the sample were identified and then subjected to antimicrobial susceptibility testing based on the Mycobacteria species identified. See p. 1652 column 1 under "nucleic acid procedures" and "antimicrobial susceptibility testing" and under "results" first paragraph and bridging paragraph)

As to claim 13, the process of instant step b as set taught by Cooksey et al involves a comparison with instant step (a) as taught by Cooksey et al. See p. 1652 table 1

As to claim 14-15, the microorganism is Mycobacteria and the antimicrobial is an antibiotic. See p. 1652 table 1.

As to claim 18-19, analyzing the microorganism's nucleic acid comprises determination of at least a part of the microorganism's genome sequence using PCR to identify a 123 base pair region of IS6110 or PCR-RFLP analysis of the oxy R region of the genome sequence of *M. tuberculosis*. See p. 1651 column 1 under "nucleic acid procedures".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peck et al. US 5,789,173 Aug. 4 1998 in view of Kohne et al. US 5,738,988 April. 14, 1998.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's nucleic acid.

As to claim 1, Peck et al teaches a process for analyzing a biological sample (human body fluids, blood), comprising:

Incubating specimens of said samples in media embedded with antimicrobial agents of serial dilution concentration (pre-determined concentration) for a short time (pre-determined time period) to create differential microbial counts and amplifying the differential microbial

counts by in vitro microbial DNA replication (assessing the number of microorganisms in the sample at the end of the pre-determined time period and analyzing the micro-organism's nucleic acid). See column 3 lines 18-34 and lines 56-61. Peck teaches step instant step (a) involving identifying a microorganism present within said sample by analyzing the microorganism's nucleic acid in column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two micro-wells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed".

As to the instant claim limitation "wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species", identification of a microorganism in the sample as taught by Peck et al *is* an identification of the species of the microorganism identified. The is because a microorganism identified is a micro-organism species.

As to claim 2-5, Peck et al teaches step a and step involving nucleic acid hybridization assay involving DNA amplification from the microorganism using polymerase chain reaction PCR. See DNA amplification primers in column 4 lines 38-45, column 5 lines 56-67 to column 6 lines 1-4, column 10 claims 1 and 11-13).

As to claim 6, Peck et al teaches primers specific to microorganism of interest column 4 lines 38-45 and column 10 claims 17-18.

As to claim 7-9, Peck et al teaches analyzing of the microorganism's DNA and teaches analysis of the 16S rRNA via analysis of the 16s rRNA gene. See column 10 claim 17...wherein

in vitro DNA replication amplifies a target DNA nucleotide sequence which encodes for the 16S rRNA gene.

As to claim 10, Peck et al teaches step A as set forth above and teaches that specimens from different human systems require different treatments and teaches the removal of pathogens from blood and precipitation of pathogens from blood (column 4 lines 46-47 and lines 52-58).

As to claim 13, Peck et al teaches instant step a and instant step as set forth above and teaches comparison step a and step b: column 2 lines 17-21… "identification of the pathogen, however, can be done in parallel by conventional methods, if necessary" and column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two micro-wells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed" (i.e. a control well without antibiotics but with DNA amplification primers specific for fungi and mycobacteria).

As to claim 14, Peck et al teaches that the microorganism is a fungi or a bacterium: column 4 lines 38-45: …in order to distinguish bacterial infection from fungal or mycobacterial infection when the results show resistance to all the antibacterial agents being tested two micro-wells containing no antibiotics but DNA amplification primers specific to fungi and mycobacteria respectively, are needed"

As to claim 15, Peck et al teaches that the antimicrobial is an antibiotic or an antimycotic (antifungal such as fluconazole, nystatin or amphotericin b). See column 4 lines 24-33).

Peck et al does not teach the use of a probe or a labeled probe or teach that step a and b comprises determination of at least a part of the microorganism's genome sequence.

Kohne et al teaches a process for detecting the presence and quantitating microorganism species in a sample using probes or labeled probes complementary to RNA such as ribosomal RNA (r-RNA) present in said microorganism. See column 1 lines 23-44, column 4 lines 46 to 54, lines 63 to 67, column 5 lines 1-7, and column 6 lines 17-67.

Kohne et al further teaches analyzing biological clinical samples to determine the effect of antimicrobials on a microorganism in a clinical sample comprising plating the sample on an agar plate containing antimicrobial agent (obviously at a pre-determined concentration), incubating said agar plates containing said sample and antibiotic to allow for growth of the microorganism, and assessing the number of bacteria in the sample plated on said agar plate at the end of a pre-determined growth period. column 42 lines 8 to 67. Kohne et al teaches that this process is followed by said nucleic acid hybridization assay which used probes which hybridize with RNA of specific bacterial species. Column 12 lines 43 to 49 and 43 lines 12 to 61.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to identify the microorganisms present in the sample of Peck et al using the probes of Kohne et al and also use said probes in determining the effect of antimicrobial(s) on said identified microorganisms, with a reasonable expectation of success. This is because Kohne et al teaches probes that hybridize to rRNA sequences of widely different organisms or that hybridize to specific organisms (specific probes) which can be used to detect or identify a microorganism in a sample (column 12 lines 34 to 49) and which can also be used in to indicate the growth of microorganisms in the presence of antimicrobial agents i.e. Kohne et al teaches that culture of organisms in the presence of an agent or agents which completely inhibit growth will not show an increase in RNA with time, while cultures which are partially

inhibited by such an agent will show a slower rate of RNA accumulation and a culture which is not inhibited will show the same rate of RNA increase as the control culture which does not contain the agent. See column 42 lines 18-40. Thus, the identification of a microorganism and the rate of RNA accumulation in a microorganism in the presence of antimicrobial agent is performed by using said probes that hybridize to at least part of the microorganisms genome sequence i.e. RNA analysis (instant claim 18).

7. Claims 1-9 and 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooksey et al. Journal of Clinical Microbiology, May 2002, p. 1651-1655 in view of Kohne et al. US 5,738,988 April. 14, 1998.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's

nucleic acid; wherein step b) involves a nucleic acid hybridization assay; wherein the microorganisms' RNA is analyzed; wherein the RNA is rRNA; wherein the process comprises the use of a probe or labeled probe.

Cooksey et al teaches a process for analyzing a biological sample, comprising the steps of

-identifying a microorganism present in specimen samples from patients (see p. 1652 column 1 under "bacterial isolates" and "nucleic acid procedures")

-determining the effect of one or more antimicrobial e.g. antibiotics on a microorganisms from the sample by adding said antimicrobials at predetermined concentration to a sample, incubating the sample in the presence of said antimicrobials for a predetermined time period under conditions that allow some growth of the microorganism (i.e. plating on Middlebrook and Cohn 7H10 agar containing the antimicrobials), and assessing the number in the sample at the end of the pre-determined period (see p. 1652 column 1 under "antimicrobial susceptibility testing" and p. 1652 column 2 table 1);

-wherein identifying a microorganism present in the sample comprises identifying a microorganism species by PCR (polymerase chain reaction) or PCR-RFLP (PCR-restriction fragment length polymorphism), in the instant case Cooksey et al identifies *Mycobacterium bovis* and *Mycobacterium tuberculosis* in samples collected from patients (see p. 1652 p. 1652 column 1 under "bacterial isolates" and "nucleic acid procedures" and first paragraph under "results" section)

-wherein steps (a) and (b) are performed by analyzing the microorganisms nucleic acid. See p. 1652 table 1 for analysis of the antimicrobial resistance of *Mycobacterium tuberculosis complex* (MTC) nucleic acid compared to the RFLP pattern

As to claim 2, Cooksey et al teaches a nucleic acid hybridization assay (PCR or PCR-RFLP) for identifying the microorganism in the samples.

As to claim 4-6, Cooksey et al teaches instant step (a) as set forth above involving amplification of nucleic acid from the microorganism (PCR or PCR-RFLP) using primers specific to the Mycobacteria of interest. See p. 1652 column 1 under "nucleic acid procedures".

As to claim 7, the process of Cooksey et al as set forth above teaches analysis of the microorganisms DNA. See p. 1652 table 1 for RFLP.

As to claim 12, Cooksey et al teaches that the types of Mycobacteria species in the sample were identified and then subjected to antimicrobial susceptibility testing based on the Mycobacteria species identified. See p. 1652 column 1 under "nucleic acid procedures" and "antimicrobial susceptibility testing" and under "results" first paragraph and bridging paragraph)

As to claim 13, the process of instant step b as set taught by Cooksey et al involves a comparison with instant step (a) as taught by Cooksey et al. See p. 1652 table 1

As to claim 14-15, the microorganism is Mycobacteria and the antimicrobial is an antibiotic. See p. 1652 table 1.

As to claim 18-19, analyzing the microorganism's nucleic acid comprises determination of at least a part of the microorganism's genome sequence using PCR to identify a 123 base pair region of IS6110 or PCR-RFLP analysis of the oxy R region of the genome sequence of *M. tuberculosis.* See p. 1651 column 1 under "nucleic acid procedures".

Cooksey et al does not teach that the process of determining the effect of one or more antimicrobials involves a nucleic acid hybridization assay; does not teach analysis of the

microorganism's RNA wherein the RNA is rRNA and does not teach the process comprises the use of a probe or labeled probe.

Kohne et al teaches a process for detecting the presence and quantitating microorganism and other organisms in a sample using probes or labeled probes complementary to RNA such as ribosomal RNA (r-RNA) present in said microorganism. See column 1 lines 23-44, column 4 lines 46 to 54, lines 63 to 67, column 5 lines 1-7, and column 6 lines 17-67. Kohne et al further teaches analyzing biological clinical samples to determine the effect of antimicrobial on a microorganism (e.g. *Mycobacterium tuberculosis)* in a clinical sample comprising plating the sample on an agar plate containing antimicrobial agent (inherently at a pre-determined concentration), incubating said agar plates containing said sample and antibiotic to allow for growth of the microorganism, and assessing the number of bacteria in the sample plated on said agar plate at the end of a pre-determined growth period. column 42 lines 8 to 67. Kohne et al teaches that this process is followed by said nucleic acid hybridization assay which used probes which hybridize with RNA e.g. rRNA of specific bacterial species. Column 12 lines 43 to 49 and 43 lines 12 to 61.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to identify the microorganisms present in the sample of Cooksey et al using the probes of Kohne et al and also use said probes in a process comprising determining the effect of antimicrobial(s) on said identified microorganisms, with a reasonable expectation of success. This is because Kohne et al teaches probes that hybridize to rRNA sequences of widely different organisms or that hybridize to specific organisms (specific probes) which can be used to detect or identify a microorganism e.g. *M. tuberculosis* in a sample (column 12 lines 34 to 49,

column 42 lines 18-67) and which can also be used to indicate the growth of microorganisms in the presence of antimicrobial agents in a nucleic acid hybridization assay i.e. Kohne et al teaches that culture of organisms in the presence of an agent or agents which completely inhibit growth will not show an increase in RNA with time, while cultures which are partially inhibited by such an agent will show a slower rate of RNA accumulation and a culture which is not inhibited will show the same rate of RNA increase as the control culture which does not contain the agent. See column 42 lines 18-40. Thus, the identification of a microorganism and the rate of RNA accumulation in a microorganism in the presence of antimicrobial agent is each performed by using said probes that hybridize to at least part of the microorganisms genome sequence i.e. RNA/rRNA analysis.

8. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooksey et al. Journal of Clinical Microbiology, May 2002, p. 1651-1655 and Kohne et al. US 5,738,988 April. 14, 1998, as applied to claims 1-9 and 12-19, further in view of Bruno et al. Journal of Molecular Recognition, Vol. 9, 474-479 (1996) cited in IDS.

The claims are drawn to a process for analyzing a biological sample, comprising the steps of:

(a) identifying a micro-organism present within the sample; and

(b) determining the effect of one or more antimicrobial(s) on a micro-organism from the sample, wherein determining the effect of one or more antimicrobials comprises adding an antimicrobial at a pre-determined concentration to a sample, incubating the

sample in the presence of the antimicrobial for a pre-determined time period under conditions that allow some growth of the micro-organism, and assessing the number of microorganisms in the sample at the end of the pre-determined time period; wherein identifying a micro-organism present in the sample comprises identifying a micro-organisms species

wherein steps (a) and (b) are performed by analyzing the micro-organism's

nucleic acid; wherein the microorganisms are extracted from the sample prior to step (a);

wherein microorganisms are extracted by immunomagnetic separation.

The combination of Cooksey et al and Kohne et al does not teach extraction of microorganism from the patient samples i.e. cerebrospinal fluids (CSF, see p. 1652 column 1 under "bacterial isolates") by immunomagnetic separation.

Bruno et al teaches that immunomagnetic separation and concentration of specific target ligands or particles, such as bacteria ... from complex mixtures such as bone marrow, blood and other body fluids is now a widely accepted technique (see abstract, first sentence) and immunomagnetic separation has the advantage of concentration of the target antigens in complex media (see p. 474 column 1 under "introduction").

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to separate pathogen/microorganisms from CSF samples of Cooksey et al and Kohne et al as combined before the identification of the microorganisms using immunomagnetic separation because Bruno et al teaches that immunomagnetic separation and concentration of specific target ligands or particles, such as bacteria from complex mixtures such as body fluids is a known and widely accepted technique (see abstract, first sentence) and immunomagnetic separation has the advantage of concentration of the target antigens in complex

media (see p. 474 column 1 under "introduction"). Thus, resulting in the instant invention with a reasonable expectation of success.

Status of Claims

Claims 1-19 are rejected. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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